REMARKS

Issues raised by the examiner are rendered moot by the foregoing. This is not to imply any agreement with any aspect of the office action. The previous claims met all requirements of 35 U.S.C.

Language in claims 109 and 111 regarding the enteric coating composition is based on conventional knowledge of the chemical composition of the enteric material utilized in Example 2, i.e., EUDRAGIT® L 30 D-55. This can be seen from the attached data sheets describing this well known enteric material, e.g., "EUDRAGIT L, Aqueous Dispersion, Data Sheet (Info LD-2/e), EUDRAGIT L 30 D" (two pages), at page 1, top and column 1; and "EUDRAGIT L, Aqueous Dispersion, Standards Sheet (Info LD-7/e), EUDRAGIT L 30 D" (two pages), at page 1, top and columns 1 and 2. (The notation "55" in the nomenclature used in the specification is an equivalent of the older nomenclature L 30 D, "55" simply referring to the pH (5.5) at which the enteric material becomes soluble.) Conventional values of area under the curve (AUC), maximum plasma concentration (C_{max}) and the time to achieve C_{max}, i.e., T_{max}, are taken directly from Figs. 7 and 8 of the application. Approximate AUC values were obtained by conventional weighing techniques and C_{max} and T_{max} by visual curve reading. The term "about" has its usual meaning in the field, e.g., roughly $\pm$ 20%, for example as used by FDA in its determinations of bioequivalency. The values from Figs. 7 and 8 are d-amphetamine levels to one of ordinary skill in the art, the mixture of amphetamine salts ("MAS" (page 16, lines 15-16)) used in the examples being the "mixture of four amphetamine salts" in ADDERALL® (page 4, lines 15-17) whose relative salt content is known. (See the PDR excerpts of record and the d-amphetamine plasma curves in the prior art, e.g., in Suc et al. also of record.)

Applicants maintain their position as set forth in the response submitted on October 24, 2002. The cited prior art does not render obvious any of the previously pending claims or the claims being added at this time, for the reasons set forth in the mentioned amendment. Thus, there is nothing in the prior art which would motivate a skilled worker to formulate the claimed active ingredients in the manner recited in the claims. See the case law described in the last response. Moreover, the previous claims and the current claims meet all requirements of 35

U.S.C. 112. The patent specification provides plentiful information whereby a skilled worker could, without undue experimentation, produce formulations which meet the requirements of the claims, e.g., the plasma levels as defined previously or in the current claims.

As for the comments of the Examiner on pages 4-6, the law has long been that functionality at the point of novelty is acceptable. *In re Swinehart, 439 F.2d 210, 169 U.S.P.Q 226 (CCPA 1971).* Even if this doctrine were relevant and even if there were limits to it, these would not apply here, either for the previous claims or the current claims. The public is clearly informed of the limits of the claimed subject matter in both cases and of how to carry out the invention as claimed. Moreover, it is not clear to what multiple medication levels the Examiner refers. As is true for any open formulation claims, medicaments other than those specifically recited are included. However, the statute merely requires that the invention as recited in the claims be disclosed, not every possible variation which might be included. The Examiner also raises the issue of unexpected results. Applicants have not previously or now chosen to rely on any unexpected results.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

Brion P. Heaney, Reg. No. 32,542
Anthony J. Zelano, Reg. No. 27,969
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410
Attorney Docket No.: PHARMA-142 P1

Date: April 21, 2003
K:\Pharma\142\p1\Reply

Data Sheet
(into LD-2/e)

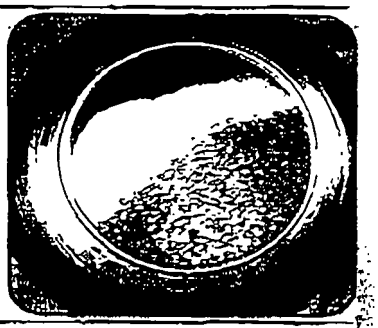
Eudragit™ L

Aqueous Dispersion

for enteric film coatings

soluble in intestinal juice from pH 5.5 upwards

"Methacrylic Acid Copolymer" USP/NF



EUDRAGIT L 30 D is an aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester. The polymer corresponds to USP/NF, "Methacrylic Acid Copolymer, Type C"

It is soluble in a neutral to weakly alkaline milieu by forming salts with alkalis, thus affording **enteric** film coatings which are **soluble in intestinal juice.**

EUDRAGIT L 30 D

Characteristics of the product

Form in which supplied
Aqueous dispersion containing **no plasticisers**

Appearance
A milky-white liquid of low viscosity

Odour
Weakly sour

Content
30 % of dry lacquer substance

Acid value
315 mg KOH/g of dry lacquer substance

Relative density
d_4^{20} : 1.07

Viscosity 20° C
7 mPa · s

pH
2.5

Storage
Keep well sealed, free from frost, at a temperature not higher than 30°C, preferably 5–25°C. At least one years' storage life following delivery from our plant at Weiterstadt. Once the can has been opened, the contents should be processed as soon as possible.

Containers
Blue polyethylene cans, 5 kg net and 30 kg net.

Possible applications*

Coating of **tablets and pills:** colourless and transparent; coloured with pigments

- to improve shelf life – protection against moisture, light and air – coatings stable under tropical conditions
- for resistance to gastric juice
- for resistance to gastric juice with delayed drug release in the intestine when thicker layers are applied
- to isolate porous cores
- for the production of film coatings for lozenges and troches

Coating of **capsules:**

- for resistance to gastric juice
- for protection against atmospheric influences
- to improve shelf life

Coating of **pellets, granules, powders:**

- for resistance to gastric juice
- for resistance to gastric juice with delayed drug release in the intestine when thicker layers are applied
- for isolation of incompatible ingredients
- to improve shelf life

Granulation with EUDRAGIT L 30 D:

- for isolation of incompatible ingredients
- to improve shelf life

* For the more important uses technical application pamphlets "EUDRAGIT L 30 D – Examples of application" are available.

Characteristics of the film

Colourless and transparent films are formed from EUDRAGIT L 30 D when plasticisers (polyethylene glycols, propylene glycol, triacetin, etc.) are present. These films are insoluble in pure water, in buffer solutions below pH 5.0, and also in natural and artificial gastric juices. They are soluble in the neutral to weakly alkaline region of the digestive tract, i.e. in the intestines, in pancreatic or intestinal juice, and in buffer solutions above pH 5.5.

Alternatives

It is recommended that dosage forms which are extremely sensitive to water be subcoated first of all with the EUDRAGIT L lacquer substances dissolved in organic solvents.
Commercial presentations **EUDRAGIT L12.5/12.5 P** or the solid substance **EUDRAGIT L 100** (into L-2, 2e, 4/e).

Diluents

EUDRAGIT L 30 D is miscible with water in any proportion; the milky-white appearance is retained

For special purposes the dispersion can also be mixed with water-miscible organic solvents such as acetone, ethyl alcohol and isopropyl alcohol, or with mixtures of these solvents. The lacquer substance is precipitated initially, and then dissolves in the excess organic solvent

Film coatings which are soluble in water are obtained by neutralising the EUDRAGIT L 30 D dispersion with alkalis. With acids, the lacquer substance is again precipitated.

Incompatibilities

Aqueous synthetic-polymer dispersions are manufactured by emulsion polymerisation in which the monomers are finely distributed by the addition of emulsifiers in water. After the formation of macromolecules in the form of latex particles, adsorption of emulsifiers on to the surface of the particles prevents agglomeration. External influences can disturb the emulsifier adsorbed at the surface of the latex particles and cause their agglomeration. Initially this takes the form of aggregation, but eventually, on becoming more pronounced, it is reflected in the formation of spots, and finally leads to **coagulation.**

Coagulated dispersions cannot be redispersed and are **unusable.**

Coagulation can be caused by electrolytes, pH changes, organic solvents, foam formation, the effects of heat and frost, finely dispersed pigments, and also severe shearing gradients in high-speed stirrers and mills. EUDRAGIT L 30 D is also highly incompatible with magnesium stearate.

Processing

To enhance the elasticity of the EUDRAGIT L 30 D films, the addition of plasticisers is strongly recommended (polyethylene glycols, propylene glycol, triacetin, dibutyl phthalate, citric acid esters)

The addition of 10% of plasticiser, calculated on the amount of dry lacquer substance, is generally adequate, but this can be increased to 25% if necessary without any adverse affects on the functioning of the lacquer film.

The addition of **separating substances** (talc, pigments) decreases the tendency to agglutinate and produces more uniform surfaces.

Generally speaking, water-sensitive cores should be subcoated beforehand with a sealing layer of the organic lacquer solution EUDRAGIT L 12.5, particularly when EUDRAGIT L 30 D is being applied by the **fractional application process.** For this purpose, the application of 20 g of lacquer solution per kg of tablets is adequate; with tablets of average shape and size, this is equivalent to the application of 0.25% of dry lacquer substance calculated on the quantity of tablets being coated. EUDRAGIT L 30 D can subsequently be applied by fractional application as the undiluted 30% dispersion.

Uniform and smooth film coatings are obtained by **spray application** of the dispersion diluted to some 20%. This procedure may be carried out in coating pans or by the fluidised-bed system.

Fluidised-bed systems are in actual fact more suitable for coating **pellets, granules** and **powders.** Highly diluted dispersions with separating substances added should be used to reduce the formation of agglomerates.

Pneumatic spray guns operating at pressures of 0.5–3 bar are particularly suitable for spraying purposes. **Airless spraying systems** can also be employed for production batches of more than 80 kg. With granulation processes EUDRAGIT L 30 D should preferably be sprayed on in the mixing vessel.

Pigments, preferably the so-called **food-colouring** lacquers, are suitable for **colouring** EUDRAGIT L 30 D films, these are finely dispersed in water and then mixed with a 20% or so dispersion of EUDRAGIT L 30 D.

As finely dispersed pigments can lead to **coagulation** of the dispersion, emulsifiers (Tween 80) or stabilisers (polyethylene glycols, carboxymethyl cellulose, polyvinylpyrrolidone) must be added to the pigment suspensions. The addition of antifoam agents (silicone emulsions) to the pigment suspension is recommended to reduce foam formation during dispersion.

Three to four parts of pigments, talc and other formulation aids can be used to one part of EUDRAGIT L 30 D dry lacquer substance.

To **polish** the finished film coatings, approximately 10% aqueous solutions of polyethylene glycol can be used.

Amount of lacquer required

Generally speaking, the amounts of lacquer required depend on the surface area of the cores to be coated.

The approximate values in mg of dry lacquer substance per cm^2 of surface are

to produce coats simply for sealing purposes
0.2–0.5 mg/cm^2

to produce coats which are stable on storage and which are to be used for special protective purposes
1–2 mg/cm^2

to produce **enteric coatings**
3–5 mg/cm^2

With medium size tablets (8 mm diameter, 4 mm high, 200 mg weight) the latter quantities give a 3–5 per cent weight increase.

Average requirements for the production of enteric film coatings:

150 g EUDRAGIT L 30 D per kg of tablets

300 g EUDRAGIT L 30 D per kg of granules, pellets, powder

For more detailed calculation formulae, see the prospectus "EUDRAGIT L – Application in the Production of Pharmaceutical Preparations" (Info LD-1/e).

Additional prospectuses

EUDRAGIT L 30 D – Application in the Production of Pharmaceutical Preparations (Info LD-1/e)

EUDRAGIT L 30 D – Quality Norms and Methods of Analysis (Info LD-7/e)

EUDRAGIT L 30 D – Examples of Application (Info LD-11/e)

Publications (Reprints available)

K. LEHMANN and D. DREHER „Anwendung wäßriger Kunststoffdispersionen zum Überziehen von Arzneiformen" [The use of aqueous polymer dispersions for coating dosage forms] Die Pharmazeutische Industrie, *34*, 894–899 (1972)

D. DREHER „Der Einsatz der verschiedenen Acrylharzlacke für Arzneiformen mit gesteuerter Wirkstoffabgabe" [Film coatings on acrylic resin basis for dosage forms with controlled drug release] Pharma International, 1975 (1/2), 9

K. LEHMANN „Magensaftresistente und retardierende Arzneimittelüberzüge aus wäßrigen Acrylharzdispersionen" [Enteric and retard coating of pharmaceutical preparations with aqueous acrylic resin dispersions] APV Informationsdienst [APV Information Service] *2*, (4), 255 (1975)

Standards Sheet
(Info LD-7/e)

Eudragit™ L

Aqueous Dispersion

for enteric film coatings

soluble in intestinal juice from pH 5.5 upwards

"Methacrylic Acid Copolymer" USP/NF

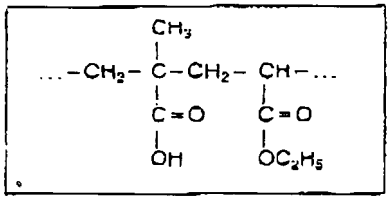
Quality norms and methods of analysis

for

EUDRAGIT™ L 30 D

Chemical structure

EUDRAGIT L 30 D is the aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The polymer corresponds to USP/NF, "Methacrylic Acid Copolymer, Type C".



The ratio of the free carboxyl groups to the ester groups is approximately 1:1.

The mean molecular weight is 250 000.

The preparation contains no plasticisers, and it is recommended that these be added to enhance the characteristics of the film.

EUDRAGIT L 30 D is preferentially used to afford an enteric coating to drugs which is, however, soluble in intestinal juice

Commercial forms, content

EUDRAGIT L 30 D
Aqueous dispersion, milky-white liquid of low viscosity with a weakly sour odour.

Content
28.5–31.5% dry polymer substance.

Approximately 1 g of the dispersion is dried 5 h at 110°C according to Ph. Eur. I, "Loss on drying", method e.

On drying, the dispersion must form a clear film.

Properties

The polymer meets the requirements of USP/NF. In addition, the dispersion contains small amounts of emulsifiers.

Solubility
The aqueous dispersion is miscible with water in any proportion; the milky-white appearance is retained. A clear or slightly opalescent, viscous solution is obtained on mixing one part of EUDRAGIT L 30 D with five parts of acetone. The same results are obtained on mixing with ethyl alcohol or isopropyl alcohol; the lacquer substance is first of all precipitated, but then dissolves in the excess organic solvent.

A clear or slightly opalescent, viscous liquid is obtained on mixing one part of EUDRAGIT L 30 D with two parts of sodium hydroxide 1 N.

Test solution
The EUDRAGIT L 30 D dispersion as obtained is used as the test solution. The dispersion should be filtered through a fine sieve with openings of some 0.1 mm before use in order to remove any coagulum or film particles.

Formation of film
10 g of EUDRAGIT L 30 D are mixed with 0.3 g of triacetin. On pouring the dispersion on to a glass slide, transparent lacquer films are formed once the water has evaporated.

Acid value
315 mg of KOH per g of dry lacquer substance

Standard limits: 300–330.

The acid value (AV) specifies how many mg of KOH are necessary for the neutralisation of the acid groups contained in 1 g of dry substance (DS).

The test is carried out according to Ph. Eur. I, "Non-aqueous titrations/ Acids". The end-point is determined potentiometrically according to Ph. Eur. I, "Potentiometric titrations" 0.5 g of EUDRAGIT L 30 D are dissolved in 90 ml of isopropyl alcohol and 10 ml of water. 0.1 N tetramethylammonium hydroxide solution (TMAH) is employed as the titrant.

$$\text{AV (mg KOH per g of DS)} = \frac{\text{ml 0.1 N TMAH} \cdot 561}{\text{weight of sample (g)} \cdot \%\ \text{DS}}$$

Viscosity
mPa · s: max. 100
measured with a Brookfield viscometer, adapter/30 at 20°C according to Ph. Eur. I, 2nd Ed., "Viscosity/ Rotating viscometer method".

pH
2.0–3.0
according to Ph. Eur. I, "Potentiometric determination of pH".

Relative density
d_4^{20}: 1.060–1.070
according to Ph. Eur. I, "Relative density".

Coagulum content
A stainless steel sifting cloth with openings of 0.09 mm is accurately weighed. 100 g of EUDRAGIT L 30 D are filtered through this sifting cloth. The cloth is washed with distilled water until a clear filtrate is obtained and dried to constant weight at 80°C and the weight of the filtration residue is determined.

Standard limit: max. 1000 mg ≙ 1%.

Identity testing
Proof of identity is established by IR spectroscopy of a film formed from EUDRAGIT L 30 D, 15 µm thick.
To produce the film, one drop of EUDRAGIT L 30 D is placed on a glass slide which is then covered with a water-insensitive crystal disc (AgCl, KRS 5). By lightly pressing on and then removing the crystal disc, a clear film will be obtained after a drying time of some 15 minutes.

Shown in the figure presented below are the characteristic bands for C = O vibrations of the carboxyl groups at 1705 cm^{-1} and ester groups at 1735 cm^{-1}, further ester vibrations at 1150–1180 and 1250–1270 cm^{-1}, strongly associated OH vibrations in the range of 2500 and 3500 cm^{-1}, and CH_x vibrations at 1385, 1450, 1475 and 2940–2990 cm^{-1}

Purity testing
1. **Sulphated ash:** max. 0.4% according to Ph. Eur. I, "Sulphated ash" or USP XXI, page 1192, "Residue on ignition".
2. **Heavy metals:** max. 20 ppm of Pb, according to USP XXI, page 1189, "Heavy metals", method II.
3. **Arsenic:** max. 2 ppm according to USP XXI, page 1187, "Arsenic", method II.

The tests are carried out on 1 g of EUDRAGIT L 30 D.

Detection in dosage forms
Since the polymer substance contained in EUDRAGIT L 30 D resembles EUDRAGIT L 100, the methods described in the publication „Analysengang zum Nachweis von Tablettier- und Dragierhilfsstoffen" [Analytical procedure for the detection of excipients in tabletting and film coating] by L. Ehrhardt and H. Sucker (Pharm. Ind. 32, 92–97, 176–178, 296–300 [1970]) can be used for the detection of EUDRAGIT L 30 D in dosage forms.

Storage
Store between 5 and 25°C. EUDRAGIT L 30 D should not be subjected either to frost or to temperatures above 30°C. Once the can has been opened, the content should be processed as soon as possible. Keep dispersions in well-closed containers.

Storage life: at least one year from the date of delivery if the above conditions are adhered to